REMARKS

Claims 24-27, 36-44, 47, 52 and 55-59 are pending. Claims 98 and 99 have been added, as supported by paragraph 0092. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier. Applicant respectfully requests further consideration of the present application in light of the following remarks.

All of the prior rejections have been withdrawn in favor of new rejections based on the same combinations of references. Thus, claims 24-26, 36-38, 44, 47, 52, and 55-57 are rejected under 35 U.S.C. §103(a) based on United States Patent No. 5,789,554 in view of Maloney *et al.* and Li *et al.* Claims 24-27, 36-38, 44, 52, and 55-57 are rejected under 35 U.S.C. §103(a) based on United States Patent No. 5,789,554 in view of Maloney *et al.* and United States Patent No. 5,106,955. Claims 24-26, 36-42, 44, 52, and 55-57 are rejected under 35 U.S.C. §103(a) based on United States Patent No. 5,789,554 in view of Maloney *et al.* and United States Patent No. 5,686,072 and PCT publication WO 95/09917. Claims 24-26, 36-39, 44, 52, and 55-57 are rejected under 35 U.S.C. §103(a) based on United States Patent No. 5,789,554 in view of Maloney *et al.* and European Patent Application No. 510949. Claims 24-27, 36-38, 43, 44, 52, and 55-59 and are rejected under 35 U.S.C. §103(a) based on United States Patent No. 5,789,554 in view of Maloney *et al.* and United States Patent No. 5,698,178. Claims 24-27, 38, 43, 44, 52, 55-59 are rejected under 35 U.S.C. §103(a) based on WO 96/04925 in view of Maloney *et al.* and United States Patent No. 5,698,178. When queried as to the difference over the prior rejections, Examiner Harris explained in a voice mail message that the new rejections differ from the previous rejections because they rely upon *In re Kerkhoven*.

However, the present rejections still rely on Maloney as the basis for suggesting a combination of antibodies. While Examiner Harris does not make statements in the body of her Action relating to "conventional therapies" as in previous actions, this still forms the basis for her rejection. This is clear inasmuch as the examiner cites the last paragraph on page 2465 of Maloney, which is the paragraph mentioning the use of anti-CD20 "in combination with conventional therapies." Applicant has provided abundant evidence for the record from experts in the field that "conventional therapies" at the time of the Maloney article, circa 1994, were chemotherapies, not antibody therapies, and this evidence stands unrebutted on the record. Hence the present rejection is improper on this basis alone, as there still is no support in the record suggesting therapy using a combination of antibodies.

Moreover, the case of *In re Kerkhoven* clearly can be distinguished from the claims presently at issue. *In re Kerkhoven* is cited for its statement that "it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

At issue in *Kerkhoven* were claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents. The combination was held to be *prima facie* obvious. *Kerkhoven* related to the combination of two spray-dried detergents, and was concerned with obtaining an end product with good flow characteristics. To this end, separate slurries of two detergents were treated in a spray drying apparatus. This was an improvement over prior art methods in which two detergents were mixed together in one slurry and then spray dried together. The Board and the CCPA found the broad claim in *Kerkhoven* to have been obvious over the prior art process. More particularly, the Board noted that "one skilled in the art, knowing that individual detergents or certain mixtures of detergents produce particles having good free-flowing characteristics, would understand that the detergents desired in the final composition may be dried separately and then mixed."

The focus in Kerkhoven's application was a solution to problems with the flowing and storage properties of powdered detergents that contained two detergent ingredients, *i.e.*, with physical properties of the mixture. It is straightforward to predict the flowability property of combining two spray-dried detergents. There was nothing to suggest any difference in the ability of the resulting detergent in cleaning ability, a property in which some unpredictablilty might inhere. Indeed, as noted by Judges Miller and Markey, "the uncertainty and unpredictability often associated with the chemical arts is not present here." These are products that are used outside the body, and detergents that are not spray-dried have been combined for years, as noted in the background of Kerkhoven's application. Thus, the Board and the CCPA were justified in finding the end result, a free-flowing combination of detergents, to have been obvious, although the CCPA did find one of Kerkhoven's claims to recite unobvious subject matter.[1]

The claims at issue in this case present a much different situation. In biology and chemistry, two separate agents can be antagonistic, agonistic, additive, or synergistic, and no one can predict the result until it is tried. In fact, MPEP 2144.06, which is cited by the examiner, cautions that

[1] This claim issued in US 4,274,974.

obviousness of a combination of compositions taught by the prior art to be useful for the same purpose does not always hold, citing *In re Geiger*, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987) ("Based upon the prior art and the fact that each of the three components of the composition used in the claimed method is conventionally employed in the art for treating cooling water systems, the board held that it would have been *prima facie* obvious, within the meaning of 35 U.S.C. 103, to employ these components in combination for their known functions and to optimize the amount of each additive.... Appellant argues... hindsight reconstruction or at best... 'obvious to try'.... We agree with appellant."). Thus, it is apparent that the Office cautions examiners to determine whether it is obvious to combine two compositions on a case-by-case basis.

In the present case, a combination of antibodies is claimed: a conjugate of a human, humanized or chimeric anti-CD22 antibody, and a naked anti-CD20 mAb. The result of combining two different antibodies is not predictable. Often it is not known whether an antibody is agonistic or antagonistic, leading to unpredictability as to the result of a combination. Moreover, different antibodies may occupy nearby positions on the cell membrane and compete for sites so that no additive effect is seen. Also, when combining two antibodies it is not known whether the toxicities are additive, which would lead to an unacceptable level of toxicity. Thus, a skilled person would not have been able to predict whether a combination of antibodies would have an additive or synergistic effect or whether the antibodies would interfere with each other so that the combination would have a reduced effect. It was also a possibility that since both antibodies affect normal B-cells, they could act in concert to be more toxic than either alone.

Surprisingly, applicants have discovered that a combination of anti-CD22 and anti-CD20 antibodies as presently claimed produces an unpredictable increase in efficacy with no adverse toxic effect. This unexpected result has been documented in published papers.

Leonard *et al.* disclose a combination therapy using epratuzumab, an anti-CD22 antibody, with rituximab, an anti-CD20 antibody. *J. Clin. Oncol.*, 23(22): 5044-5051 (2005), copy appended. The results achieved with each antibody separately are compared to the results with the combination. On page 5048, column 1, it is reported that the objective response (OR) rate of rituximab in patients with indolent non-Hodgkin's lymphoma (NHL) is 48%, with 6% having a complete response (CR). In the passage bridging pages 5048, column 2 to page 5049, column 1, treatment with epratuzumab is discussed. Here, 43% of patients with follicular NHL and 15% of patients with diffuse large B-cell lymphoma achieved an objective response.

The results for the combination of rituximab and epratuzumab are given on pages 5046-5047. The objective response was 63% in patients with NHL, with 56% of patients achieving a complete response. The level of complete responses is therefore significantly higher than for rituximab alone. Furthermore, in the passage headed "Response to Treatment," the authors explain that the median duration of remission for indolent and aggressive NHL had not yet been reached.

In the second and third paragraphs of column 1 on page 5049, the authors explain that the combination of epratuzumab and rituximab may be more efficacious than either antibody used alone. The authors also report that the toxicity to the combination antibody regimen was similar in nature and degree to that previously reported with rituximab monotherapy. This is quite surprising, as it might have been expected that toxicity would be greater for a combination than from a single antibody.

Thus, Leonard *et al.* teach that the combination therapy is more efficacious than either monotherapy, but that toxicity is similar in nature and degree. Particularly noteworthy is the passage bridging columns 1 and 2 of page 5049, which reports CR rates for patients with recurrent NHL of 56% for indolent follicular NHL and 42% for DLBCL, which is higher than the rates reported for rituximab alone in comparable dosing schedules (about 20%).

Stein *et al.* disclose results with another anti-CD20 antibody, IMMU-106, in combination with epratuzumab. *Clin. Cancer Res.*, 10:2868-2878 (2004), copy appended. The activity of this antibody is compared with that of rituximab and with a combination of IMMU-006 and rituximab. Figure 8 relates to an *in vitro* assay measuring the anti-proliferative effects of IMMU-106, epratuzumab, and the combination of IMMU-006 and epratuzumab. Figure 8 shows that IMMU-106 alone caused a 53% inhibition of proliferation, epratuzumab had no effect and the combination caused an 83% inhibition of proliferation. This shows that the combination has a synergistic effect which clearly could not have been predicted based on the activity of either antibody alone. Figure 9 shows the results of *in vivo* experiments in mice and shows that the combination prolongs survival.

On page 2876, column 2, third paragraph, the authors state that the combination is "synergistic." More particularly, the authors suggest that the increased efficacy may be due to "additive or synergistic effects on signaling events initiated by the anti-CD20 and anti-CD22 MAbs, although there may be little or no antiproliferative effects of the anti-CD22 MAb when given alone."

The results in Leonard and Stein demonstrate that a combination of anti-CD20 and anti-CD22 antibodies produces an increase in efficacy that could not have been predicted. By extension, this means that a toxic agent conjugated to one of the two antibodies can be affected by the administration of the other antibody as a naked antibody. That is, the present invention goes beyond the complementation of targeting two different antigens, with the naked antibody actually affecting the uptake of the antibody bearing the toxic agent. The results show that prior administration of one antibody, *e.g.*, epratuzumab, actually upregulates the expression and activity of rituximab or IMMU-106, as detailed by Stein (2004) and further elucidated in the Discussion section of Carnahan (2007), a copy of which is appended. The converse also is true: treatment with a CD20 naked antibody upregulates expression of CD22 and thereby increases the uptake of conjugated anti-CD22 antibody.

It was particularly unexpected that combinations of anti-CD20 and anti-CD22 immunoconjugates would be more effective when administered in combination, either concurrently or sequentially, is because the anti-CD22 antibody internalizes very rapidly. See, *e.g.*, Carnahan (2003), a copy of which is appended. Therefore, the duration of the antibody on the cell surface and its antitumor activity may be of a very brief nature. However, when used to deliver a therapeutic, such as a conjugated radionuclide or drug, its action is not dependent on the naked antibody, but rather internalization of the therapeutic. By combining the killing action of the anti-CD20 antibody which can upregulate the CD22 antigen expression and also decrease the number of lymphoma cells available for killing with the anti-CD22 immunoconjugate, an increased therapeutic efficacy is achieved. This has not been suggested in prior publications on uses of either conjugated or unconjugated anti-lymphoma antibodies. In studies with radiolabeled anti-CD20 antibodies, for example, predosing with a naked version of the same anti-CD20 antibody was undertaken in order to saturate CD20 antigen sites on normal tissues, thus enhancing targeting and uptake in tumor of the radiolabeled anti-CD20 antibody. This is the mechanism employed by Bexxar, a regimen employing tositumomab and Iodine I^{131} tositumomab. There has been, however, no suggestion of predosing with anti-CD20 antibody prior to giving a radiolabeled anti-CD22 antibody.

In summary, it would not have been obvious to combine an immunoconjugate of an anti-CD22 antibody and a naked anti-CD20 antibody. There is no suggestion in the record that would lead a skilled artisan to combination antibody therapy. Moreover, the case of *In re Kerkhoven* clearly has been distinguished. Finally, applicant has made of record evidence, in the form of

several articles, that the combination of antibodies produces results that were unexpected. For all of these reasons, the present claims are believed to be allowable over the outstanding rejections.

Claims 24-27, 36-44, 47, 52, and 55-89 are provisionally rejected under the doctrine of obviousness-type double patenting over claims 24-44 of co-pending application No. 10/314,330. The examiner states that the rejection is maintained pending an indication of allowable subject matter.

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

If there are any problems with this response, Applicant's attorney would appreciate a telephone call. In view of the foregoing, it is believed none of the references, taken singly or in combination, disclose the claimed invention. Accordingly, this application is believed to be in condition for allowance, the notice of which is respectfully requested.

Respectfully submitted,

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